28. A vaccine according to Claim 12 wherein said adjuvant is either an antibody that binds cell surface receptor CD40, or a part of said antibody that is effective at binding CD40. - -

REMARKS

Reconsideration of this Application is respectfully requested. Claims 1, 2, 13, 15, and 17 have been amended, and new Claims 24-28 have been added to more particularly point out and distinctly claim the subject matter of the invention. Support for the amendments to the claims can be found throughout the Specification as originally filed, including in the original claims. Further support for the amendments to Claims 2, 15, 17, and for new Claims 24-28 can be found on Page 19, lines 11-24 of the Specification as originally filed. More particularly, further support for Claim 24 can be found on Page 20 lines 1-8 of the Specification as originally filed, and further support for Claim 25 can be found on line 23 of Page 20 through line 12 of Page 21 of the Specification as originally filed. Claims 1-10, 12, 13, and 15-28 remain pending and are presented for reconsideration. No new matter has been entered.

Rejections under 35 U.S.C.§ 112, first paragraph:

The Examiner has rejected Claims 15-23 for an asserted lack of enablement. Whereas the Examiner admits that the Specification enables the claims for "antibodies that bind CD40 or CD40L" and parts thereof, as well as "CD40L" as "adjuvants adapted to stimulate B lymphocyte CD40", the Examiner asserts that the claims are not enabled for any potential adjuvant.

The Applicant respectfully traverses the Examiner's rejection. The Applicant has amended the claims to more particularly point out and distinctly claim the subject matter of the invention. The Specification as originally filed fully enables the skilled artisan to practice the invention as claimed.

In view of the above and foregoing, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph are respectfully solicited.

Rejection under 35 U.S.C. §102 (e):

The Examiner has rejected Claims 1-4, 8-10, 12, 13, 15, and 16 as being anticipated under 35 U.S.C. §102(e) by Mond *et al.*, U.S. Patent No. 5,874,085 or alternatively by Mond *et al.*, U.S. Patent No. 5,932,427. The Examiner asserts that the '085 and '427 patents teach the production and use of multivalent vaccines that comprise CD40L antigens to stimulate B cell response to a variety of T cell dependent and independent antigens. The Examiner further asserts that the fusion protein of the present invention is not viewed as a further limiting of the claims, since according to the Examiner, the cited references teach a variety of means to cross-link adjuvants and activators.

The Applicants respectfully traverse the Examiner's rejections. As defined by the Federal Circuit,

"[t]o anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject-matter."*PPG Industries, Inc. v. Guardian Industries Corp.*, 37 USPQ2d 1618 (Fed. Cir. 1996). "Anticipation requires identity of the claimed process and a process of the prior art; the claimed process, including each step thereof, must have been described or embodied, either expressly or inherently, in a single reference." *Glaverbel Société Anonyme v. Northlake Marketing & Supply Inc.*, 33 USPQ2d 1496,1498 (1995).

In the present case, neither the '085 patent nor the '427 patent teach every element of the invention as claimed. The '085 patent discloses compositions and methods for optimizing IgA class switching in B lymphocytes. The '427 patent describes compositions comprising granulocyte-macrophage colony stimulating factor (GM-CSF, interleukin-3 (IL-3)) for use in stimulating the release of antibodies by B-lymphocytes. The '427 patent teaches an *in vitro* assay system for identifying compositions useful for stimulating the release of antibodies by B lymphocytes such as the combination of GM-CSF and a cytokine (IL-3) in promoting antibody secretion by B lymphocytes. There is no disclosure of vaccines that include antigens that are joined together with CD40 antibodies or CD40 ligands in either patent.

Furthermore, Column 3, lines 32-34 of the '085 patent specifically states that stimulants such as lypopolysaccharide (LPS) and CD40 ligand activate B cell proliferation and Ig secretion without isotype switching. In addition, the '085 patent teaches that a cytokine, such as exogenous cytokines TGF-β, IL-4, and either IL-5 or IL-2, is required for isotype switching.

Indeed, the various vaccine structures and components listed in Table 2, Column 16 of the '085 patent all contain a cytokine either added in a simple admixture or conjugated to the multivalent carrier and/or antigen. Consistently, the only independent claim in the '085 patent includes at least one cytokine which stimulates IgA class switching, along with a B cell activator selected from the group consisting of CD40 ligand and LPS. Moreover, each of the passages in the '427 patent cited by the Examiner, namely Column 8, lines 60-65, and Column 11, lines 4-8, confirm the requirement of an exogenous cytokine in the vaccine. In direct contrast to the '427 patent and the '085 patent, however, the claimed immunogenic compositions and vaccines of the present invention do not require exogenous cytokines. Therefore, for the reasons indicated above, neither the '427 Patent nor the '087 patent anticipate the present invention.

In view of the above and foregoing, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(e) are respectfully solicited.

Rejection under 35 U.S.C. §103:

The Examiner has also rejected Claims 1-10, 12, 13, and 15 as being obvious over U.S. Patent Nos. 5,874,085 and 5,932,427, in view of U.S. Patent Nos. 5,247,069 and 5,961,974, and further in view of the known methods in the art.

The Examiner admits that Mond *et al.* differ from the claimed invention by (i) not disclosing the use of anti-CD40 antibodies as adjuvants in the immunogenic compositions, and (ii) not teaching the production of the immunogenic compositions as a fusion proteins. However, the Examiner asserts that Ledbetter *et al.* (Patent No. 5,247,069) teach the use of Bp50-specific antibodies as adjuvants. The Examiner further asserts that Armitage *et al.* teach that oligomeric CD40 ligands and cross-linked anti-CD40 antibodies are agonistic. The Examiner concludes that it would have been obvious to make the immunogenic compositions and the fusion constructs of the present invention. The Examiner further asserts that it was known that the antibodies were useful as vaccine adjuvants. Finally, the Examiner asserts that the kits comprising the cells and nucleic acids encoding the immunogenic compositions (including fusion proteins comprising the CD40 ligand/anti-CD40 antibody and antigen) are also obvious in view of the cited art.

The Applicants respectfully traverse the Examiner's rejections. Mond *et al.*, U.S. Patent Nos. 5,874,085 and 5,932,427 not only do not anticipate the present invention, they teach away from the present invention. Indeed, Mond *et al.*, as indicated above, teach that the CD40 ligand activates B cell proliferation and Ig secretion without isotype switching and that an exogenous cytokine is required for isotype switching.

Section 2141.02 of the MPEP states:

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert denied*, 469 U.S. 851 (1984).

Therefore, the present invention is not obvious in view of the Mond patents, *i.e.*, U.S. Patent Nos. 5,874,085 and 5,932,427.

Furthermore, the disclosures of Ledbetter *et al.*, and/or Armitage *et al.*, U.S. Patent Nos. 5,247,069 and 5,961,974, respectively, do not obviate the present invention. Indeed, Ledbetter *et al.*, (U.S. Patent No. 5,247,069) particularly states that the anti-Bp50 mAb (which the Examiner has pointed out corresponds to the anti-CD40 antibody) **could not** activate B-cells (see Column 18, line 21). Therefore, the '069 patent also teaches away from the present invention.

Finally Armitage *et al.*, (US Patent No. 5,961,974) simply teaches the sequences of the CD40 ligand (CD40-L), antibodies (particularly monoclonal antibodies) which recognize the CD40 ligand and pharmaceutical composition comprising said antibodies. There is no reference to the use of antibodies as adjuvants in the formulation of vaccines. Indeed, the data disclosed in the '974 patent demonstrate the ability of anti-CD40-L monoclonal antibodies to bind CD40-L and thereby inhibit B-lymphocyte cell proliferation (*see* Figure 17). Consistently, the '974 patent states that anti-CD40 antibodies require IL-4 and cross-linking to mediate B-cell proliferation and immunoglobulin secretion (*see* Column 5, lines 57-62). Therefore, the present invention is also not obvious in view of Armitage *et al.*, US Patent No. 5,961,974.

Furthermore, the present invention is not an obvious extension of the current immunological dogma. For example, a conjugate of the CD40 antibody and a given antigen would not be expected to be effective in enhancing immune responses. Indeed, it would be anticipated that the antigen-anti-CD40 conjugate would be internalized by antigen presenting cells and then processed into short peptides for preparation of MHC class II presentation. Since

the anti-CD40 antibody would be proteolyzed along with the antigen in the APC, the anti-CD40 antibody would be expected to be unable to stimulate B cells through the CD40 receptor. Consistently, as stated previously, a recent attempt by researchers from Stanford University to use CD40L as an adjuvant did not include the step of cross-linking the antigen to CD40L [Wong *et al.*, *J. Immunology* **162**:2251-2258 (1999)]. In addition, the vaccines of the present invention unexpectedly promote both Ig secretion and isotype switching. Indeed, the skilled artisan is only brought to the present invention by the Applicant's disclosure. Thus, neither Mond *et al.*, U.S. Patent No. 5,874,085, Mond *et al.*, 5,932,427, Armitage *et al.*, US Patent No. 5,961,974, nor Ledbetter *et al.*, U.S. Patent No. 5,247,069 either alone or when taken together teach the invention as claimed and therefore the present invention is not obvious in view of U.S. Patent Nos. 5,874,085, 5,932,427, 5,961,974, or 5,247,069.

In view of the above and foregoing, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are respectfully solicited.

In view of the foregoing amendments and remarks, reconsideration and early allowance of Claims 1-10, 12, 13, and 15-28 are respectfully requested. No additional fees are believed to be necessitated by the foregoing amendments. However, should this be erroneous, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or credit any overages. Should the Examiner feel that a telephone conference would facilitate resolution of any of the above issues, he is invited to telephone the undersigned attorney.

In view of the above and foregoing, reconsideration and withdrawal of the outstanding grounds of rejection and early allowance of the claims as amended is believed to be in order and are respectfully solicited.

Respectfully submitted,

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PENDING CLAIMS AFTER JULY 3, 2000 AMENDMENT

1. (Thrice Amended) An immunogenic composition consisting essentially of an adjuvant and an antigen;

wherein said adjuvant and said antigen are joined together;

wherein said adjuvant is selected from the group consisting of an antibody that binds cell surface receptor CD40; a part of said antibody that is effective at binding CD40, and a CD40 ligand; and

wherein when said adjuvant binds to CD40 of a B-lymphocyte cell said adjuvant helps in activating said B-lymphocyte cell.

2. (Twice Amended) A vaccine consisting essentially of an adjuvant and an antigen;

wherein said adjuvant is selected from the group consisting of an antibody that binds cell surface receptor CD40, a part of said antibody that is effective at binding CD40, and a CD40 ligand;

wherein when said adjuvant binds to CD40 of a B-lymphocyte cell said adjuvant helps in activating said B-lymphocyte cell; and

wherein the vaccine promotes Ig secretion and isotype switching.

3. (Amended) A vaccine according to Claim 2 wherein said antigen is a T-cell dependent or T-cell independent antigen, or part of said T-cell dependent or T-cell independent antigen.

4. (Amended) A vaccine according to Claim 2 wherein said adjuvant is a CD40 ligand.

5. (Amended) A vaccine according to Claim 2 wherein said adjuvant is an antibody raised against said CD40, or a part of said antibody that is effective at binding CD40.

6. A vaccine according to Claim 5 wherein the antibody is monoclonal.

7. A vaccine according to Claim 5 wherein the antibody is humanised.

8. A vaccine according to Claim 3 wherein said antigen is soluble.

9. A vaccine according to Claim 3 wherein said antigen is a protein.

10. A vaccine wherein said antigen is a polysaccharide.

12. (Amended) A vaccine according to Claim 3 wherein said antigen is a protein or part thereof, and said antigen is fused to said adjuvant so as to provide a fusion protein.

13. (Twice Amended) A vaccine according to Claim 12 further comprising at least one cytokine.

15. (Twice Amended) A method for the manufacture of a vaccine capable of enhancing immunity comprising

(a) selecting a suitable T-cell dependent and/or T-cell independent antigen, or parts thereof, and

(b) associating or combining said antigen with an adjuvant; wherein said adjuvant is selected from the group consisting of an antibody that binds cell surface receptor CD40, a part of said antibody that is effective at binding CD40, and a CD40 ligand;

wherein when said adjuvant binds to CD40 of a B-lymphocyte cell said adjuvant helps in activating said B-lymphocyte cell; and

wherein the vaccine promotes Ig secretion and isotype switching.

16. A method according to Claim 15 wherein said vaccine is capable of enhancing T-cell independent immunity.

17. (Twice Amended) A kit for the manufacture of a vaccine capable of enhancing T-cell independent or T-cell dependent immunity comprising a cell expressing a selected T-cell dependent and/or T-cell independent antigen, or parts thereof, and an adjuvant selected from the group consisting of an antibody that binds cell surface receptor CD40, a part of said antibody that is effective at binding CD40, and a CD40 ligand;

wherein when said adjuvant binds to CD40 of a B-lymphocyte cell said adjuvant helps in activating said B-lymphocyte cell; and

wherein the vaccine promotes Ig secretion and isotype switching.

18. (Amended) A kit according to Claim 17 wherein said vaccine is capable of enhancing T-cell independent immunity.

19. (Amended) A kit according to Claim 17 wherein one or both of said antigen and adjuvant is provided with a secretion signal whereby expression of one or both of said antigen or adjuvant results in secretion of one or both of said antigen or adjuvant from said cell.

20. (Amended) A kit according to Claim 17 wherein the expression of said antigen and adjuvant is adapted such that a single fusion protein can be manufactured by said cell.

21. (Amended) A kit according to Claim 20 wherein said single fusion protein is adapted for secretion from said cell.

22. (Amended) A nucleic acid molecule encoding the fusion protein according to Claim 12.

23. A nucleic acid molecule encoding a vaccine according to Claim 2.

24. A vaccine consisting essentially of an adjuvant and one or more antigens;

wherein said adjuvant is selected from the group consisting of an antibody that binds cell surface receptor CD40, a part of said antibody that is effective at binding CD40, and a CD40 ligand;

wherein when said adjuvant binds to CD40 of a B-lymphocyte cell said adjuvant helps in activating said B-lymphocyte cell; and

wherein the vaccine promotes Ig secretion and isotype switching.

25. A vaccine comprising an adjuvant and an antigen;

wherein said adjuvant is selected from the group consisting of an antibody that binds cell surface receptor CD40, a part of said antibody that is effective at binding CD40, and a CD40 ligand;

wherein when said adjuvant binds to CD40 of a B-lymphocyte cell said adjuvant helps in activating said B-lymphocyte cell;

wherein the vaccine promotes Ig secretion and isotype switching; and

wherein the vaccine does not comprise an exogenous cytokine.

26. The vaccine of Claim 25 wherein said adjuvant and said antigen are joined together.

27. The vaccine of Claim 24 wherein said adjuvant and said antigen are joined together.

28. A vaccine according to Claim 12 wherein said adjuvant is either an antibody that binds cell surface receptor CD40, or a part of said antibody that is effective at binding CD40.